UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,515	09/25/2003	Peter Adorjan	47675-155	1178

22504 7590 12/13/2007

DAVIS WRIGHT TREMAINE, LLP/Seattle
1201 Third Avenue, Suite 2200
SEATTLE, WA 98101-3045

EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
12/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,515	ADORJAN ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-52* is/are pending in the application.

4a) Of the above claim(s) *18-24,26-43 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,25,44 and 48-52* is/are rejected.

7)☒ Claim(s) *1 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 September 2007 has been entered.

Accordingly, claims 1-11 and 13-52 are pending in the instant Office action.

Claims 1-11, 13-17, 25, 44, and 48-52 are examined in the instant Office action.

Claims 18-24, 26-43, and 45-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 16 December 2005.

Comments

Claim 17 has the incorrect status identifier of "Withdrawn." It is currently being examined and has not been withdrawn by the Office. Applicant is encouraged to carefully review the claim status identifiers for correctness in future amendments.

The indicated allowability of claims 13-17 is withdrawn in view of newly applied rejections over the reference(s) to Curtis et al. [Ann. Hum. Genet, 2001, volume 65, pages 95-107]. Rejections based on the cited reference(s) follow.

Claim Objections

The objection to claim 2 because of informalities is withdrawn in view of amendments to the claim filed on 26 September 2007.

Claim 1 is objected to because of the following informalities:

Line 17 of claim 1 has the phrase "each pair of classes or pair or unions the at least two..." This phrase is grammatically inconsistent.

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 is dependent from claim 1 and repeats limitation d of claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-17, 25, 44, and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "the method as recited in claim 1, wherein the selecting step of g)..." in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Step g) of claim 1 is no longer a "selecting" step.

Claim Rejections - 35 USC § 102

The rejections of claims 1-10 and 48 under 35 U.S.C. 102(b) as being anticipated by Tornaletti et al. [Oncogene, 1995, volume 10, pages 1493-1499] are withdrawn in view of amendments to the set of claims filed on 26 September 2007.

Claim Rejections - 35 USC § 103

The rejections of claims 1, 2, 10-11, 49-50, and 52 under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. in view of Gaasterland et al. [Nature Genetics, March 2000, volume 24, pages 204-206] are withdrawn in view of arguments filed on page 12 of the Remarks of 26 September 2007.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35 U.S.C. 103 Rejection #1:

Claims 1, 2, 10-11, 49-50, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. [Oncogene, 1995, volume 10, pages 1493-1499] in view of Laird et al. [US PGPub 2004/0033490 published 19 February 2004] in view of Gaasterland et al. [Nature Genetics, March 2000, volume 24, pages 204-206].

Claim 1 is drawn to a method for selecting epigenetic features comprising the following the following ten steps:

--collecting and storing biological samples with mammalian genomic DNA;

--collecting and storing available phenotypic information about the biological samples so as to define a phenotypic data set;

--defining at least one phenotypic parameter of interest;

--dividing the biological samples into at least two disjunct phenotypic classes of interest using the defined phenotypic classes of interest;

--selecting pairs or pairs of unions of classes from the disjunct phenotypic classes of interest;

--defining, for each selected pair, an initial set of epigenetic features of interest;

--analyzing the defined epigenetic features of interest of the biological samples so as to generate an epigenetic feature data set for each pair;

--selecting relevant epigenetic features of interest and/or combinations of epigenetic features of interest of the defined epigenetic features of interest, the relevant epigenetic features of interest and/or combinations of epigenetic features and/or combinations of epigenetic features of interest being relevant for epigenetically-based prediction of each pair of classes or pair of unions for the at least two phenotypic classes of interest;

--performing epigenetically-based prediction of each pair of classes or pair of unions of classes using a machine learning classifier.

The article of Tornaletti et al., entitled, "Complete and tissue-independent methylation of CpG sites in the p53 gene: implications for mutations in human cancers," states in the first sentences of its abstract:

> CpG dinucleotides are the target of about one third of transition mutations found in human genetic diseases and tumors. Methylation at these sites is thought to be the cause of these genetic changes through spontaneous deamination of 5-methylcytosine.

Collection and isolation of human genomic DNA are described in the "Materials and Methods" section on pages 1497-1498 under "DNA and cell culture" and "DNA isolation, base-specific modification and cleavage." (i.e. step (a) of instant claim 1).

The phenotype selected in this study is the presence or absence of certain types of cancers (two disjunct phenotypic classes of interest). The biological samples are

divided into portions specific to each type of cancer phenotype examined. The caption to Figure 1 on Tornaletti et al. states on page 1495:

> Figure 1. Genomic sequencing and methylation analysis of the human p53 gene. The autoradiogram shows the analysis of exon 5, upper strand. Lanes 1-2: C+T- and C-specific Maxam-Gilbert sequencing reactions of unmethylated p53-PCR products; lanes 3-11: C-specific Maxam –Gilbert sequencing reactions of genomic DNA isolated from the following sources: FIB, human skin fibroblasts; KER, normal human epidermal keratinocytes; LUNG, normal human bronchial epithelial cells; MAM, human mammary epithelial cells; COL, normal colonic mucosa cells; BLO, human peripheral blood lymphocytes; HeLa, HeLa S3 cells; CEM, leukemia CEM cells; T-47D, human breast carcinoma cells.

Consequently, Figure 1 of Tornaletti et al. collects and stores phenotypic information about the samples (step (b) of claim 1), defines the phenotypic parameters (i.e. cancers of interest; step (c) of claim 1), divides the samples into at least two disjunct phenotypic classes of interest (step (d) of claim 1).

Figure 1 of Tornaletti et al. comprises pairs of classes of disjunct types of phenotypes (i.e. different pairs of cancer types; step (e) of claim 1).

Tornaletti et al. continues in column 2, lines 36-40, by stating:

> Five out of six p53 mutation hotspot codons contain CpG dinucleotides (165, 245, 248, 273, and 282) indicating methylation-driven deamination of 5-mC as a major source of G:C→A:T transition mutations at CpG dinucleotides.

Consequently, Tornaletti et al. teaches an initial set of methylations (i.e. epigenetic features of interest). Figure 1 of Tornaletti et al. analyses these epigenetic features of interest by showing gels indicating respective methylations at each CpG dinucleotide of interest (165, 245, 248, 273, and 282) for each pair of phenotypic classes of interest (steps (f) and (g) of claim 1).

However, Tornaletti et al. does not teach the step of predicting phenotypic classes of interest from epigenetic data sets (step (h) of claim 1) or defining new

epigenetic features of interest based on epigenetic features of interest (step (i) of claim 1). In addition, Tornaletti et al. does not use machine learning classifiers to aid in predicting phenotypic information from epigenetic properties (step (j) of claim 1).

The study of Laird et al. discloses prediction of esophageal adenocarcinoma from epigenetic features of interest.

Claim 1 of Laird et al. is drawn to making a prediction of the esophageal cancer based on the methylation state of the genomic CpG sequences of a given profile of the epigenetic features of interest (i.e. step (h) of instant claim 1). Claim 6 in Laird et al. is based on claim 1 of Laird et al. wherein a new set of epigenetic features of interest are disclosed based on the list in claim 1 of Laird et al. (step (i) of instant claim 1).

While Tornaletti et al. and Laird et al. in combination predict phenotypes based on epigenetics, both studies do not use machine learning classifiers to aid in the process (step (j) of claim 1).

The study of Gaasterland et al., entitled, "Making the most of microarray data," states in the abstract:

> The impact of microarray technology on biology will depend on computational methods of data analysis. A supervised computer-learning method using support vector machines predicts gene function from expression data—and shows promise.

Gaasterland et al. explain the purpose of using machine learning classifiers in the bottom three columns of page 204:

> Microarray assays can measure the transcriptional effects of changes in gene function under different conditions. They can reveal genes that characterize tissue type, developmental stage, or responses to environmental conditions or genetic modifications. Microarray assays will therefore become a general feature of experimental protocols in genetics and cell physiology. As array data burgeon, new questions arose: if we, as a research community, collect all array hybridization data on a central location, can we assign new genes of unknown function to known functional classes? Can we correlate gene expression with gene function? Can we find new

> classes of co-regulated genes? Can we extract complete gene regulatory networks from microarray gene expression data?
>
> Computation is our only hope.... Support vector machines (SVMs) a supervised computer-learning method, [is used] to train a 'classification machine' to recognize new genes that are similar in expression pattern to groups of genes that are similar in expression pattern to groups of genes known to be co-regulated.

Figure 1 on page 205 of Gaasterland et al. illustrates the process of machine classification with a threshold. The caption states:

> Fig 1. A support vector machine (SVM) is a computational entity that accepts positive and negative training examples of a topic to be learned. As is 'learns', it draws a hyper-plane [threshold] which maximally separates input data points into two classes, members (green) and non-members (red). Here, input data is shown in three-dimensions...

Consequently, Gaasterland et al. uses machine learning classifiers to better classify genes and expression patterns of genes.

Claim 2 is further comprises repeating steps based on the new set of epigenetic features of interest defined in the ninth step.

Claims 1-7 of Laird et al. repeat the epigenetic prediction and analysis with various different sets of epigenetic features of interest.

Claim 3 is further limiting wherein the biological samples include cellular components which contain DNA. Figure 1 of Tornaletti et al. displays genomic sequencing of sources of DNA.

Claims 4 and 5 are further limiting wherein the sample can be taken from breast tissue. The last three lines of column 2 of page 1497 of Tornaletti et al. indicate human breast carcinoma genomic DNA tissue as being used.

Claim 6 is further limiting wherein the phenotypic parameter of interest is selected from a kind of tissue and gene expression. Claim 7 is further limiting wherein the epigenetic features of interest include cytosine methylation sites on DNA. Figure 1 of Tornaletti et al. illustrates gene expression and cytosine methylation from various tissue types.

Claim 8 is further limiting wherein there is preliminary knowledge about the correlation between epigenetic features of interest and their correlation with phenotypic parameters of interest. The introduction on page 1493 of Tornaletti et al. indicates prior art that shows a correlation between mutations in the DNA (i.e. cytosine methylations and disease).

Claim 9 is further limiting wherein an accuracy or significance is likely to decrease by exclusion of epigenetic feature data.

Eliminating a lane from Figure 1 of Tornaletti et al. (i.e. the first or second lanes), makes the process of determining how cytosine methylations of p53 DNA affect the phenotypic outcome of the presence of cancer qualitatively much more difficult. This process described is repeated iteratively for various types of tissue shown in Figure 1 of Tornaletti et al.

Claim 10 is further limiting wherein the fourth step of the first claim is performed as to divide the biological samples into two disjunct phenotypic classes of interest.

Figure 1 of Tornaletti et al. divides the phenotypes into disjunct types of cancer phenotypes.

Claim 11 is further limiting wherein a machine classifier is utilized for prediction. As described above, the study of Gaasterland et al. utilizes machine learning classifiers.

Claim 48 is further limiting wherein the iterations in claim 1 are performed until a defined number of epigenetic features of interest are selected. Claim 49 is further limiting wherein features of interest with a combination score greater than a defined threshold are selected.

Claims 1-7 of Laird et al. repeat the epigenetic prediction and analysis with various different sets of epigenetic features of interest. For example, claims 7 and 10 of Laird et al. narrow the original set of epigenetic features in claim 1 and select a specified number of epigenetic features of interest. Claim 10 of Laird et al. also specifies a certain threshold in methylation level to be met in order to qualify as a methylated gene.

Claim 50 is further limiting comprising determining an optimal number of epigenetic features of interest using a crossvalidation of a machine learning classifier on test subsets of epigenetic feature data. Claim 52 is further limiting comprising training

the machine learning classifier. Figure 2 of Gaasterland et al. illustrates the training of the machine learning classifier. Figure 1 of Gaasterland et al. illustrates training as well, showing validation of separation of disjunct phenotypes.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the study of the relation of cytosine methylation to human cancer of Tornaletti et al. by use of the epigenetic prediction study of Laird et al. by use of the machine classification study of Gaasterland et al. where the motivation would have been that while Tornaletti et al. separated phenotype classes of interest and defined sites on the p53 gene which when methylated result in human cancer, Laird et al. describes cancer detection solely from epigenetic features in a way that increases the efficiency and amount of information that governs the conditions in each sample characterization [see for example, paragraph [0015] of Laird et al.] Furthermore, Gaasterland et al. expands on using machine classifiers to more efficiently and computationally analyze microarrays with many different samples (see for example, pages 204-205 of Gaasterland et al.)

Response to arguments:

Applicant's arguments filed 26 September 2007 have been fully considered and they are persuasive. However, Applicant's arguments are moot in view of the new ground(s) of rejection.

35 U.S.C. 103 Rejection #2:

Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. in view of Laird et al. in view of Gaasterland et al. as applied to claims 1-11, 48-50, and 52 above, and further in view of Curtis et al. [Annals in Human Genetics, volume 65, pages 95-107, 2001].

Claim 13 is further limiting wherein after definition of a candidate epigenetic feature selection and feature criterion selection, the candidate sets of epigenetic features are ranked and the highest ranking epigenetic features are chosen.

Claim 14 is further limiting wherein a set of all subsets of epigenetic features of interest are chosen.

Claims 15 and 16 are further limiting wherein each epigenetic feature set is assigned a cardinality, the highest cardinality being chosen as the epigenetic features of interest.

Claim 17 is further limiting with the additional limiting of performing the predictions of phenotype based on epigenetic features of interest using PCA.

Tornaletti et al., Laird et al., and Gaasterland et al. make obvious the use of machine learning classifiers for the purpose of predicting phenotypic properties based on epigenetic parameters, as described above. Gaasterland et al. uses PCA in column 3 of page 205 as a method of analysis which is independent of prior analysis, reduced the data set with many variables to a smaller number of uncorrelated variables.

Tornaletti et al., Laird et al., and Gaasterland et al. do not teach ranking of epigenetic feature sets using cardinalities.

The study of Curtis et al. studies SNPs and how using the epigenetic properties of SNPs can be used to predict disease (see abstract of Curtis et al.). Instead of examining a single mutation, the study of Curtis et al. investigates arrays of mutations using neural network models to achieve better power in predicting the disease outcome in a patient based on epigenetic properties (see, last full paragraph, column 2, page 98).

The top of Table 3 on page 103 of Curtis et al. tabulates and correlates (by ranking the number of mutations with the single mutation having a cardinality of "1") the outcome of single marker test and a neural network test as a function of the number of mutations. In all cases in the top of Table 3 on page 103 of Curtis et al., the result with a cardinality of one produced the best correlation between epigenetic features and disease outcome.

It would have been obvious to someone of ordinary skilled in the art at the time of the instant invention to modify the DNA methylation studies and machine classification methods of Tornaletti et al., Laird et al., and Gaasterland et al. by use of the SNP classification methods of Curtis et al. where the motivation would have been that using the network ranking and classification methods of Curtis et al. achieves better power in predicting the disease outcome in a patient based on epigenetic properties (see, last full paragraph, column 2, page 98).

Double Patenting

The provisional rejection of claims 1-2, 6-7, 11-17, 44, and 48-50 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-

2, 4-5, 9-15, 38, 42-44, respectively, of copending Application No. 10/106,269 is withdrawn in view of the abandonment of the copending application.

Conclusion

No claim is allowed.

Claims 25, 44, and 51 are free of the prior art because the prior art does not teach or suggest training errors for machine learning classifiers relating to epigenetic features, selecting epigenetic features based on the ranking resulting from the machine learning classifiers, and crossvalidation of the classifier relating to epigenetic features.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN
10 December 2007 12/10/07

/Marjorie A. Moran/
SPE, AU 1631
12/10/2007